REMARKS

Applicant respectfully requests entry of the foregoing and reconsideration of the application in light of the following remarks.

Claims 1-39 have been canceled. Claims 40-80 have been added. Claims 40-80 add no new matter. Although a few of the terms and phrases in claims 40-80 are not literally recited in the specification or in the previous claims, those terms and phrases are inherently or implicitly present in the specification and in the previous claims.[1]

Claims 40-80 have not been added to overcome the prior art rejections. The main reason for adding claims 40-80 was to conform to standard English and to enhance readability, clarity and brevity.[2]

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[1] *See generally Ex parte Holt*, 19 USPQ2d 1211, 1213 (PBAI 1991) (It is well established that the invention claimed need not be described *ipsis verbis* in order to satisfy the disclosure requirement of §112.); *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973) (By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter.); *Behr v. Talbot*, 27 USPQ2d 1401, 1407 (BPAI 1992) (It is not necessary for the application to reveal a conscious appreciation on the part of the applicants of the significance of the limitation in question.); *Ex parte Parks*, 30 USPQ2d 1234, 1236 (BPAI 1994) (Clearly, the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support....In the situation before us, it cannot be said that the originally-filed disclosure would not have conveyed to one having ordinary skill in the art that appellants had possession of the *concept* of conducting the decomposition step generating nitric acid in the absence of a catalyst.); *Ex Parte Yamaguchi*, 6 USPQ2d 1805, 1807 (PTO Bd App & Int 1987) (It is well settled in patent law that a compound and all of its properties are inseparable. Accordingly, where a compound is disclosed in such a manner as to comply with §112, 1st para., the later addition of symbols by which the compounds can be identified, classified and compared (such as x-ray diffraction spectra, graphic formula, chemical nomenclature) do not define a separate invention.); *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("[W]here no explicit description of a generic invention is to be found in the specification mention of representative compounds may provide an implicit description upon which to base generic claim language."); *In re Alton*, 37 USPQ2d 1578, 1581 (Fed. Cir. 1996) (If the specification contains a description of the claimed invention, albeit not in *ipsis verbis*, then the examiner or Board, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient.). *See also* MPEP 2163.07(a) Inherent Function, Theory, or Advantage.

[2] For example, new independent claims 40, 45 and 50 recite a denaturation step after the ligation step, whereas previous claim 1 recited a denaturation step before the first hybridization step. This does not mean Claims 40, 45 and 50 exclude denaturation before the first hybridization step. Claims 40, 45 and 50 encompass the use of single-stranded and double-stranded fragments. Since

(continued...)

Please note also that some terms in the previous claims were either explicitly in the plural form (*e.g.*, "assembly templates") or explicitly in the singular and plural form (*e.g.*, "assembly template or templates"). Now the terms appear in the implicit singular/plural form (*i.e.*, "an assembly template"). Thus, these terms encompass both the singular and the plural (*i.e.*, "an assembly template" encompasses one or more assembly templates.)

Objections to Specification

The amendments above satisfy the objections in Paragraphs 1-3 of the Office Action.

With regard to Paragraph 4 of the Office Action, Applicant thanks the Examiner for suggesting a preferred layout for the specification. However, Applicants prefer to retain the current layout.

Objections to Claims

The objectionable claims have been canceled. New claims 40-74 do not have the objectionable features recited in Paragraphs 5-7 of the Office Action.

Claim Rejections Under 35 USC 112

The claims rejected under Section 112 have been canceled. New claims 40-74 do not have the offending features recited in Paragraph 8(A)-(I) of the Office Action.

Claim Rejections Under 35 USC 102(e)

Previous claims 1-13, 15, 17-29 and 31-39 are rejected under 35 USC. 102 (e) as anticipated by US Pat No. 6,117,679 to Stemmer. However, Stemmer's method is polymerase-mediated.

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denaturation is always necessary when double-stranded fragments are to be hybridized to the template, the initial denaturation need not be explicitly recited. On the other hand, claims 40, 45 and 50 now recite denaturation after the first hybridization. The reason is to clarify that denaturation may occur prior to any further rounds of hybridization. In other words, denaturation after the first hybridization is not necessarily inherent in all embodiments of the invention, so it is recited in he claims.

Stemmer does not disclose or teach the ligation-mediated method of Applicant's previous claims or of new claims 40-74.

As stated in Applicant's specification, "The key step of the process of the invention is the step of ligation on an assembly template" (page 5, lines 2-3). The present invention differs from the prior art because the present invention does not, among other things, rely on polymerase to fill in large gaps between fragments hybridized on a template. Rather, the invention repeats hybridization as necessary until fragments hybridize in the gaps.[3] In other words, the invention does not hybridize a small number of fragments to a template and then polymerize the ends of the hybridized fragments toward each other until they are within ligatable distances. Instead, the invention iteratively cycles through rounds of hybridization so that more fragments hybridize to the template and so that the hybridized fragments grow in length (without polymerase extension), until a sufficient number fragments of sufficient lengths are within ligatable distances of each other.[4]

That Stemmer's method relies on polymerase extension is evident in the following passages:

-Col. 22, lines 24-26: "In shuffling, however, the number of the polymerase start sites and the number of molecules remains essentially the same."

-Col. 24, lines 37-38: "The annealed nucleic acid fragments are next incubated in the presence of a nucleic acid polymerase and dNTPs".

-Col. 24, lines 53-56: "The cycle of denaturation, renaturation and incubation in the presence of polymerase can be referred to as shuffling or reassembly of the nucleic acid."

Also conspicuous is the absence of relevant disclosure in Stemmer. Stemmer does not disclose features necessary for or consistent with Applicant's ligation-mediated method, such as the following:

-Ends of fragments adjacently hybridize on the assembly template.

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[3] Repeating the hybridizing step often also entails repeating the ligating and denaturing step immediately after each repetition of the hybridizing step. However, it is possible to repeat the hybridizing step multiple times before any ligating or denaturing.

[4] In typical embodiments of the invention, multiple rounds of hybridization are usually necessary. Under certain conditions, however, a sufficient number of fragments of sufficient lengths can hybridize within ligatable distances of each other. In Claims 40 and 50, the phrase "as necessary" allows for this unusual scenario. Claim 45, however, does not encompass this unusual scenario because it lacks "as necessary" and it always requires "multiple" rounds of hybridization.

-Repeating the hybridizing and ligating steps with the ligated and non-ligated fragments.

-Carrying out the hybridization and ligation steps simultaneously.

-Polynucleotides of the library share zones of homology among each other or with the assembly template. In other words, portions of the library polynucleotides are homologous to each other or complementary to the assembly template. This facilitates adjacent hybridization of the fragment ends on the assembly template.

Claim Rejections Under 35 USC 103(a)

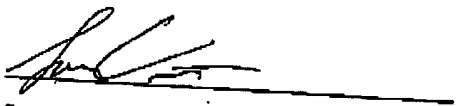
Previous claims 14 and 16 are rejected under 35 USC. 103(a) as obvious over Stemmer in view of US6,251,649 to Matsui et al. The Office Action relies on Matsui et al for disclosure of flap endonuclease that is thermoresistant and active at high temperature. Because Stemmer fails to disclose or suggest the method of any of Applicant's previous or new claims, the combination of Stemmer and Matsui et al also fails to suggest the method of any of Applicant's previous or new claims.

Applicant respectfully requests entry of the amendments and the new claims and issuance of a Notice of Allowance.

Please charge any shortage in fees due in connection with the filing of this Amendment to Deposit Account No. 50-0206, and please credit any excess fees to such deposit account.

Respectfully submitted,
HUNTON & WILLIAMS

Dated: 4-15-03

By: 

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Marked-Up Version of Amendments to Specification Paragraphs

Paragraph at page 11, third paragraph, line 26 to page 12, line 6:

The invention has for its object the generation of polynucleotide sequences liable to have advantageous properties as compared to the corresponding properties of reference sequences. The recombined polynucleotide sequences obtained at step (d) and possibly cloned are screened by any appropriate means in order to select the recombined polynucleotide sequences or the clones having advantageous properties as compared to the corresponding properties of the reference sequences. By advantageous property is understood to be, for example, the thermostability of an enzyme or its [abilityto] ability to function under conditions of pH or of temperature or of saline concentration more adapted to an enzymatic process than the control proteins usually used for said process. [Forexample] For example , such a process can be an industrial process to breakdown textile fibers or bleaching paper pulps or producing flavors in the dairy industry, the processes of biocatalysis for the synthesis by an enzymatic pathway of new therapeutic molecules, etc.

Paragraph at page 17, 2nd paragraph, lines 11-18:

The product of the five PCR was mixed and [loadedon] loaded on a 1% TBEagarose [gelAfter] gel after migration and staining of the gel with ethidium bromide, the band at 2651 bp, corresponding to the *ponB* gene amplification product surrounded by two fragments of 26 bp and 90 bp respectively, was visualized by trans-illumination under ultraviolet, and cut out with a scalpel in order to be purified with the [QUIAquick] QIAquick system (QIAGEN). [Allthe] All the DNA thus purified was eluted in 120 µl of buffer T. The concentration of this DNA was [approximatively] approximately 100 ng/µl as measured by its [absorbanceat] absorbance at 260 nm.

Paragraph at page 18, fourth paragraph, lines 21-26:

50 µl of each of the ten PCR were mixed and loaded on a 1% TBE agarose gel. After migration and staining with ethidium bromide, the band at 2572 bp, corresponding to the amplification product of the genes of the ten mutants, was cut out with a scalpel and purified with the [Quiaquick] QIAquick system (QIAGEN). [Allthe] All the DNA thus purified was eluted in 120

µl of buffer T. The concentration of this DNA was approximately 100 ng/µl according to its absorbance at 260 nm.

Paragraph at page 21, 2nd paragraph, lines 8-12:

The PCR amplification products of the RLR 1, 2 and 3 reactions were purified with the [Wizard PCR Preps] WIZARD PCR PREPS system (PROMEGA) and eluted in 45 µl of buffer T. 6 µl of each purified PCR were incubated 1 hour at 37 °C in a mixture containing 3 µl of restriction buffer C, 3 µl of BSA (1 mg/ml), 20 U of the *Eco* RI enzyme, 10 U of the *Nco* I enzyme and 15 µl of water.

Paragraph at page 21, fourth paragraph, lines 20-23:

The linearized vectors as well as the digested PCR were purified on a TBE 1% agarose gel with the QIAquick system [(QUIAGEN)] (QIAGEN). Each vector or each digested PCR was eluted in 30 µl of buffer T.